

February 28, 1973

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Dear Art,

This is just a couple of small comments on your "Atwood-Ryan-Novick" paper. Properly speaking the model does not refer especially to prokaryote evolution but rather to unicellular organisms that tend to proliferate by vegetative reproduction to the extent that linked complexes are only rarely broken up. One would guess that the same principles would apply pretty directly to paramecium (borrowing problems of macronuclear conservation) but would have rather limited application to filamentous bacteria owing to cooperation within a mycelium.

I would certainly not diminish the weight given to periodic selection in the evolution of microorganisms. (Note, for example, the discussion in the introduction to "Papers in Microbial Genetics", University of Wisconsin Press, 1952 at page xv which also reminds me that Stocker also deserves credit as a co-discoverer of periodic selection.) But in my old thinking on this question (and I have not had a new thought on it in a long time) I would classify periodic selection as a subset of the overall phenomenon of periodic sampling -- namely the prevalent habit that one ~~guesses~~ should be attributed to microbial ecology whereby large populations tend to be generated cyclicly from very small inocula, for example the single spore or single infectious organism that may initiate an epidemic. This kind of sampling will have essentially the same formal consequences for microbial evolution whether it results from mutational advantage, whether frequency dependent or not, or the exigencies of inoculation.

I was interested in the assertion, page 9, that "the major selective pressure is against the synthesis of unneeded protein". Is this a point that you would like to discuss or document in anymore detail? Do you give no role to the synthesis of redundant DNA? There are mighty few examples of auxotrophic mutants having a demonstrable selective advantage in complete media. Leffoff did describe one years ago. I understand, of course, how regulation confounds the problem but it would be good to have some empirical support even for an idea that is seemingly intuitively obvious. (I almost forgot the example that is reported in my first paper with Francis Ryan, PNAS 32:163, 1966, but perhaps for good reason since we were not able to establish a growth advantage of the leucine-dependent genotype and the actual mechanism of selection that operates there is still quite obscure.)

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One issue that needs to be thought about is whether the advantageous mutations involved in periodic selection have an absolute advantage or one which is gene-frequency dependent. Werner Brown had some evidence for the latter in some of his Brucella population. *Werner*

Page 14. Your comment about the implied random character of Fox's polypeptides: he is beginning to persuade me that the condensation is far from random, a point that has an interesting bearing on the pre-disposition of the cosmos to generate the kind of life we know.

Sincerely yours,

Joshua Lederberg
Professor of Genetics

JL/rr